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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,541	06/21/2001	Thomas J. Brennan	R-17	5815

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,541	BRENNAN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-16* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 10-21-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 9, 10 and 17-19 have been canceled. Claims 1-8 and 11-16 remain pending.

Election/Restrictions

This application contains claims 1-7 and 11-16 drawn to an invention nonelected with traverse in the reply filed on 11-12-02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim 8 is under consideration in this office action.

Claim Rejections - 35 USC § 101

Claim 8 remains rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility for reasons of record.

Claim 8 is directed toward a transgenic mouse whose genome comprises a homozygous disruption in a nucleic acid sequence comprising the nucleotide sequence set forth in SEQ ID NO:1, wherein the disruption comprises disruption of the nucleotide sequence set forth in SDEQ ID NO:1, and wherein said transgenic mouse exhibits,

relative to a wild-type mouse, a phenotype selected from the group consisting of decreased and increased pain threshold.

REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS repeated from http://www.uspto.gov/web/menu/utility.pdf

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

(Page 5-7 of utility guidelines).

> A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.
>
> (Paragraph bridging pg 32-33 of utility guidelines).

The specification teaches making PAFR -/- mice (pg 50-51).

The mice were tested in "open field testing" (pg 52, lines 16-20; Fig. 3). The specification does not distinguish the F and N generation in Table 1 or teach the strain of the wild-type control. The results of the open field test do not correlate to a useful phenotype because the "may have less anxiety in comparison to wild-type mice." In addition, only 2 PAFR -/- mice and 2 control mice were tested; one PAFR -/- mouse spent more time in the central region of the field than the control mouse, which is opposite of what is being claimed. Therefore, applicants' conclusion that the mice spent increased time in the central region of the field is flawed because the data is not statistically significant. Such an ambiguous phenotype is not specific to any disease or statistically significant because the difference observed is not significant and the mice merely "may" represent decreased anxiety.

The mice were tested in a "hot plate" test (pg 53, lines 1-5). The specification does not distinguish the F and N generation in Table 2 or teach the strain of the wild-type control. The results of the open field test do not correlate to a useful phenotype because the "may have a higher pain threshold in comparison to the wild-type mice." In addition, only 2 PAFR -/- mice and 2 control mice were tested. Therefore, applicants' conclusion that the mice displayed increase response latency to lick or fan their hind

paw on the hot plate test is based on statistically insignificant data. Such an ambiguous phenotype is not specific to any disease or statistically significant because the difference observed is not significant and the mice merely "may" represent increased pain threshold.

The specification suggests using the mice to test compounds for neurological, neuropsychological or psychotic disease, but the specification does not disclose one specific neurological, neuropsychological or psychotic disease in humans linked to a disruption in PAFR (pg 20, lines 4-8). The specification does not disclose decreased anxiety is a behavioral, neurological, psychoneurological, psychotic phenotype. Decreased anxiety and increased pain threshold do not correlate to any disease in humans.

The specification suggests using the mice to identify agents that affect PAFR function (pg 19, lines 19-21). The mouse claimed cannot be used to identify agents that act on PAFR because the mice do not express PAFR.

It was "well-known" in the scientific community at the time of filing to knock out a gene in a mouse in an attempt to determine its function; however, it was also "well-known" that the mouse may only provide clues to the function of the gene and that the mouse may not be capable of determining the function of the gene. While the mouse may have "scientific utility," "scientific utility" is not the same as "patentable utility" or a "well-established" utility.

The utility guidelines specifically state that further research is not a "substantial utility":

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of applicants' invention (with decreased anxiety or increased pain threshold) as a model of disease. Further study would be required to determine the function of the disrupted gene. The overall phenotype of the applicants' mice does not correlate to any disorder; therefore, further study would be required to determine how to use the mice to study a disorder. Thus, using the mice claimed for further research is not a "substantial utility."

Using the mice to identify the function of the knocked out gene is not a "substantial utility" or "specific utility" because the phenotype may be caused by other proteins compensating for the deleted gene. Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the

genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype may be a result of other compensating proteins and not the knocked out gene.

Using the mice to identify agents capable of altering a phenotype would require further research and is not a "substantial utility" or "specific utility" because the mouse may not be capable of identifying agents capable of treating disease. Bowery (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught, "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, lines 4-). Thus, knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or GPCR-like protein in the instant application), but the agent may not treat disease or ameliorate any symptom of disease. Further research would be required to determine how to use such an agent identified using the mouse, which is not a

"substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not the GPCR-like protein itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice.

The function of a gene may not be found by studying a knockout mouse. Mombereau (Neuropsychopharmacology, 2004, Vol. 29, pg 1050-1062) used knockout mice that had increased anxiety further study to determine the function of $GABA_B$ receptor. Mombereau did not teach how to use mice with decreased anxiety as claimed. In addition, Mombereau did not determine the function of the $GABA_B$ receptor. Mombereau administered compounds known to antagonize $GABA_B$ receptor (found in *in vitro* assays, not in the mice) to the mice. Mombereau concluded that the mice merely confirmed $GABA_B$ was involved in a molecular pathway relevant for the manifestation of anxiety or depression. Mombereau did not determine the function of $GABA_B$ receptor using the $GABA_B$ -/- mice. Mombereau concludes "we acknowledge both the inherent difficulties and the caution needed in the interpretation of behavioral analysis of genetically modified mice such as the $GABA_B(1)$ -/- mice, which have overt behavioral disturbances, in more defined tests relevant to psychopathology. Nonetheless, the current data show that even such mice can still be utilized to give important indicators of

the role of a given protein, in this case the $GABA_B$ receptor, in a molecular pathway relevant for the manifestation of anxiety or depression. These assertions can then be confirmed more parametrically using appropriate pharmacological activators and antagonists as we have done using novel $GABA_B$ receptor positive modulators and antagonists" (¶ bridging pg 1059-1060). Mombereau used the antagonists to confirm the "antidepressant-like phenotype of $GABA_B$ -/- mice pharmacologically (pg 1059, col. 1, 2nd full ¶, line 1-4). Therefore, using a mouse to merely obtain clues of the role of a protein in a molecular pathway of anxiety or to confirm the phenotype of the mouse pharmacologically as described by Mombereau is not a specific or substantial utility because it is generic to a pathway of anxiety and because it does not result in determining the function of the protein within the pathway.

Overall, the mice claimed do not have a "well-established utility" because using the mice for further research (to determine how to use the mouse as a model of non-disclosed disease, to determine the function of the gene or to identify agents capable of altering a phenotype) is not a "specific utility" or "substantial utility."

Applicants argue that one of skill would have recognized that the mouse has a well-established utility for defining the function and role of the disrupted gene, i.e. a tool in studying gene function (pg 5, last ¶; pg 6, 1st full ¶). Applicants cite MPEP 2701 II(A)(3). Applicants' arguments are not persuasive. MPEP 2701 II(A)(3) states:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of

> ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. (underlining added for emphasis)

Thus, the MPEP states a well-established utility must be specific, substantial and credible. In this case, using the mice to determine the function of the PAFR rises to the level of a scientific utility, but does not rise to the level of a specific, substantial and credible utility. Therefore, using the mice to determine the function of the PAFR gene is not a well-established utility.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure. Applicants' argument is not persuasive. The examiner has challenged all of the asserted utilities in the disclosure and has now challenged what applicants consider a "well-established" utility (not present in the disclosure.)

Applicants argue the mice have been ordered by at least four pharmaceutical companies; therefore, applicants conclude that those of skill would recognize the utility of the mice (¶ bridging pg 6-7). Applicants' argument is not persuasive. Sales may be evidence to overcome a 103 obviousness rejection, but there is no case law that establishes that "sales" are evidence of patentable utility. Evidence of sales is not evidence the mice have a "well-established" utility or a "specific utility" or a "credible utility."

Applicants argue that contrary to the product in En re Brenner, whose sole 'utility' consisted of its potential role as an object of use-testing, the mouse claimed can be used to determine the function of SEQ ID NO:1 (pg 7, 1st full ¶). Applicants' arguments are not persuasive. *In re Schoenwald*, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. The mouse claimed might only provide a clue to a pathway in which SEQ ID NO:1 is involved. This is not a specific utility because results from the tests only indicate SEQ ID NO:1 is involved in a pathway relating to decreased anxiety. The phenotype provides only a clue that SEQ ID NO:1 is generically involved in a pathway having a number of proteins. Most likely the phenotype is generic to a number of proteins within the pathway as well as proteins in other pathways that also cause decreased activity. Using the mouse to determine the function of SEQ ID NO:1 is not credible or substantial because the function of SEQ ID NO:1 may never be found using the mouse. Assuming further study of the mouse will elucidate the function of SEQ ID NO:1, the amount of research required to do so would be significant. The specification does not guide those of skill in any particular direction so that one of skill could simply perform an assay to determine the function of SEQ ID NO:1.

Claim Rejections - 35 USC § 112

Claim 8 remains rejected under 35 U.S.C. 112, first paragraph for reasons of record. Specifically, since the claimed invention is not supported by either a specific or

substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants refer to the arguments in the utility rejection, which have been addressed above.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER